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AMSTER, ROTHSTEIN & EBENSTEIN LLP
90 PARK AVENUE
NEW YORK, NY 10016

EXAMINER

HUYNH, CARLIC K

ART UNIT	PAPER NUMBER
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1617

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05/03/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/803,793

Applicant(s)

BUNTINX, ERIK

Examiner

Carlic K. Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41-91 is/are pending in the application.
- 4a) Of the above claim(s) 41-48, 51-53, 56-67, 69-71, 73-87, 90 and 91 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 49, 50, 54, 55, 68, 72, 88, and 89 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date See Continuation Sheet.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- ☐ Notice of Informal Patent Application
- ☐ Other: ____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10 August 2005 and 11 April 2007.

DETAILED ACTION

Status of the Claims

1. Claims 41-91 are pending in the application, with claims 41-48, 51-53, 56-58, 61-67, 69-71, 73-75, and 77-84 having been withdrawn from consideration, in response to the restriction requirement submitted on February 16, 2007. Accordingly, claims 49-50, 54-55, 59-60, 68, 72, 76, and 85-91 are being examined on the merits herein.

Election/Restrictions

2. Applicant's election of the claims of Group II, namely claims 49-50, 54-55, 59-60, 68, 72, 76, and 85-91, in the reply filed on March 14, 2007 is acknowledged. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 41-48, 51-53, 56-58, 61-67, 69-71, 73-75, and 77-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made in the reply filed on March 14, 2007. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants' election of (1) a single disclosed species of a second compound, (2) a single disclosed species of a third compound, and (3) Parkinson Disease as a single disclosed species of a disease or disorder, in the reply filed on March 14, 2007 is acknowledged. With respect to the

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claims referring to two compounds, applicant elects Levopoda/Carbidopa as the second compound. With respect to the claims referring to three compounds, applicant elects pipamperone and pergolide as the second and third compounds, respectively.

3. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 59-60, 76, 85-87, and 90-91 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made in the reply filed on March 14, 2007. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 49-50, 54-55, 68, 72, and 88-89 are being examined on the merits herein.

The election/restriction requirement is deemed proper and is made FINAL.

Information Disclosure Statement

The Information Disclosure Statement submitted on August 10, 2005 and April 11, 2007 is acknowledged.

Specification

4. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed

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150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the instant application contains legal phraseology, namely "said".

Appropriate correction is required.

5. The disclosure is objected to because of the following informalities: typographical errors. "Pipamperone" is misspelled on several occasions throughout the specification (for instances of incorrect spelling, see example 2 heading on page 30 and example 3 heading on page 31).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 49, 54, 68, 72, and 88-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition of pipamperone and pergolide does not reasonably provide enablement for a pharmaceutical composition of a (1) any compound with selective affinity for the dopamine-4 (D4) receptor and for the 5-HT2A receptor, and (2) any dopamine receptor or any levodopa associated with any decarboxylase inhibitor. The specification does not enable any person skilled in the art to which

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it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without *undue experimentation*. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). **Nature of the Invention:**

The rejected claim(s) is/are drawn to an invention which pertains to a pharmaceutical composition comprising:

- (a) a compound having (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors, and
- (b) a dopamine receptor agonist or a levodopa associated with a decarboxylase inhibitor, as a combined preparation for simultaneous, separate or sequential use for treating a neurodegenerative disease or disorder such as Parkinson Disease.

(2). **State of the Prior Art:**

The skilled artisan would view a pharmaceutical composition comprising (1) any compound with a selective affinity for the Dopamine-4 (D4) receptor and 5HT2A receptor and (2) any dopamine receptor or any levodopa associated with any decarboxylase inhibitor as highly unlikely. In the specification, the dopamine receptor, particularly the dopamine-4 (D4) receptor, as well as the ability of serotonin to inhibit dopamine release via its 5HT2A receptor have been implicated in Parkinson Disease (pages 1-3, paragraphs [0003] and [0006]). Levodopa has been used to treat Parkinson Disease, however, the drawback of levodopa has been their metabolism into toxic free radicals inside dopamine neurons (page 2, paragraph [0005]).

(3). **Relative Skill of Those in the Art:**

The relative skill of those in the arts of dopamine, 5HT, levodopa, and decarboxylase inhibitors is extremely high.

(4). **Predictability of the Art:**

A pharmaceutical composition comprising (1) any compound with a selective affinity for the Dopamine-4 (D4) receptor and 5HT2A receptor and (2) any dopamine receptor or any levodopa associated with any decarboxylase inhibitor is highly unpredictable. For example, Table 1 show various compounds having binding affinity for dopamine and 5HT receptors (page 34). Of those compounds, only pipamperone binds preferentially to the Dopamine-4 (D4) and 5HT2A receptors (Table 1, page 34). Thus the outcome of using any other compound from

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Table 1 would be unpredictable. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and that physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Thus, the state of the art is highly unpredictable.

(5). **Breadth of the Claims:**

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a pharmaceutical composition comprising (1) any compound with a selective affinity for the Dopamine-4 (D4) receptor and 5HT2A receptor and (2) any dopamine receptor or any levodopa associated with any decarboxylase inhibitor.

(6). **Direction or Guidance Presented:**

The guidance given by the specification as to a pharmaceutical composition comprising (1) any compound with a selective affinity for the Dopamine-4 (D4) receptor and 5HT2A receptor and (2) any dopamine receptor or any levodopa associated with any decarboxylase inhibitor is limited.

The disclosure of pipamperone having affinity for the dopamine-4 (D-4) and 5HT2A receptors is adequate (Table 1, page 34).

The disclosure of a pharmaceutical composition of pipamperone and pergolide is adequate (example 3, pages 31-33).

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(7). **Working Examples:**

The working examples in the specification show pKi values of various compounds that bind Dopamine and/or 5HT receptors (example 1 and Table 1, pages 30 and 34). Of the compounds tested, only pipamperone showed a preference to the Dopamine-4 (D4) and the 5HT2A receptors (Table 1, page 34). S18327, like pipamperone, binds to D4 and 5HT2A receptors preferentially but, unlike pipamperone, can bind to other dopamine receptors (D1, D2, and D3) (Table 1, page 34). The working examples in the specification show a clinical trial using pipamperone and pergolide for the treatment of Parkinson Disease (example 3, pages 31-33). There are no working examples using pipamperone and levodopa/carbidopa. Thus, the working examples demonstrate a pharmaceutical composition of pipamperone and pergolide.

Note that lack of a working example for prevention is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

(8). **Quantity of Experimentation Necessary:**

The specification fails to provide sufficient support for a pharmaceutical composition comprising (1) any compound with a selective affinity for the Dopamine-4 (D4) receptor and 5HT2A receptor and (2) any dopamine receptor or any levodopa associated with any decarboxylase inhibitor. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any dopamine inhibitor, dopamine agonist, and levodopa associated with a decarboxylase inhibitor having the function recited in the instant claims suitable to practice the claimed invention.

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Therefore, in view of the Wands factors, e.g. the predictability of the art, the amount of direction or guidance, and the lack of working examples discussed above, a person of skill in the art would not be able to fully practice the instant invention without *undue experimentation*.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Regarding claims 49-50, 54-55, 68, 72, and 88-89, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).
8. Claims 49-50, 54-55, 68, 72, and 88-89 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to "a composition" as "a combined preparation...for separate or sequential use". "A composition" may not be used separately.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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9. Claims 49, 54, 68, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner et al. (US 6,300,354) in view of Hubble (European Journal of Neurology Suppl. 2000. Vol. 7. Suppl. 1. pp. 15-20) and Silver et al. (Neurology. 1998. Vol. 50. Suppl. 6. pp. S18-S22).

Steiner et al. teach N-substituted azabicyclo-heptane derivatives with high affinities for D₄ and 5-HT_{2A} receptors (column 1, lines 8-10 and 13).

Steiner et al. do not teach treating Parkinson Disease specifically, a dopamine receptor agonist and a levodopa associated with a decarboxylase inhibitor.

Hubble teaches the dopamine receptor agonist pergolide as a conventional dopamine agonist used to treat Parkinson Disease (page 16).

Silver et al. teach the levodopa associated with a decarboxylase inhibitor, carbidopa-levodopa is the most effective for relieving signs and symptoms of Parkinson Disease (page S18).

To a person of skill in the art at the time of the invention, it would have been obvious to employ the N-substituted azabicyclo-heptane derivatives of Steiner et al. to contain pergolide and levodopa/carbidopa because the compounds of Hubble and Silver et al. contain pergolide and levodopa/carbidopa and according to Hubble and Silver et al., pergolide and levodopa/carbidopa are a dopamine receptor agonist and a levodopa associated with a decarboxylase inhibitor that are effective at treating Parkinson Disease.

The motivation to combine the compounds of Hubble and Silver et al. to the compounds of Steiner et al. is that the compounds of Hubble and Silver et al. are a dopamine receptor agonist and a levodopa associated with a decarboxylase inhibitor that are effective at treating Parkinson Disease.

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10. Claims 50 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mantelle (US 5,446,070).

Mantelle teaches compositions of various combinations of carbidopa, levodopa, pipamperone, and pergolide (column 33, lines 56 and 58; column 34, line 20; and column 37, line 62). This the limitations of a pipamperone and pergolide composition and a pipamperone and levodopa/carbidopa composition as recited in the instant claims are met.

Regarding the dose range of pipamperone, pergolide, and levodopa/carbidopa as recited in instant claims 50 and 55, Mantelle teaches compositions containing about 1 to about 50% by weight of the pharmaceutically active agent, which meets the limitations of the instant claims (column 10, lines 59-61). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the quantity of the pharmacological agents, namely levodopa, carbidopa, pipamperone, and pergolide, provided in a composition, according to the guidance set forth in Mantelle, to provide a composition having the desired doses of levodopa/carbidopa, pipamperone, and pergolide in the pharmaceutical composition. It is noted that “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”

In re Aller, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

11. Claims 88-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner et al. (US 6,300,354) in view of Hubble (European Journal of Neurology Suppl. 2000. Vol. 7. Suppl. 1. pp. 15-20) and Silver et al. (Neurology. 1998. Vol. 50. Suppl. 6. pp. S18-S22) as applied to claims 49, 54, 68, and 72 above, in further view of Mantelle (US 5,446,070) as applied

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to claims 50 and 55 above, and in further view of Schotte et al. (Psychopharmacology. 1996. Vol. 124. pp. 57-73).

Schottle et al. teach that pipamperone has a high affinity for 5HT_{2A} receptors and may bind to dopamine-4 (D4) receptors (page 57).

To a person of skill in the art at the time of the invention, it would have been obvious to employ the compositions of Steiner et al., Hubble, Silver et al. and Mantelle to contain pipamperone because the compounds of Schottle et al. contain pipamperone and according to Schottle et al., pipamperone preferentially binds to 5HT_{2A} receptors and dopamine-4 (D4) receptors.

The motivation to combine the compounds of Steiner et al., Hubble, Silver et al. and Mantelle to the compounds of Schottle et al. is that the compounds of Schottle et al. contain pipamperone, which preferentially binds to 5HT_{2A} receptors and dopamine-4 (D4) receptors.

Double Patenting

Obviousness-Type

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

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with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 50 and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4 of copending Application Buntinx (US 2005/0203130).

The claim of Buntinx (US 2005/0203130) is directed to a method of treating a disease or disorder comprising administering pipamperone and a second compound, which may be levodopa or a dopamine receptor agonist such as pergolide. It is noted that claims 1 and 4 of Buntinx (US 2005/0203130) are drawn to a method comprising a composition of pipamperone and a second compound, the same pipamperone and pergolide or levodopa composition as recited in instant claims 50 and 55. Since claim 4 of Buntinx (US 2005/0203130) recites that the second compound can be levodopa or a dopamine receptor agonist such as pergolide, the claims of the instant application are rendered obvious over the claims of copending Application Buntinx (US 2005/0203130).

This is a provisional double patenting rejection since the conflicting claims have not been patented.

Conclusion

13. No claims are allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh

SHENG JIN WANG
PRIMARY EXAMINER